HFA-305

MINUTES OF A MEETING
December 3, 1999

Warner Lambert meeting Re: Anticaries/Antiplaque/Antigingivitis mouth rinse

CDER Participants:
Office of Drug Evaluation V, HFD-105
Robert DeLap, M.D., Director

Division of OTC Drug Products, HFD-560
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Robert Sherman, Biologist, IDS
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Division of Dermatological and Dental Drug Products, HFD-540
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Division of Biometrics IV, HFD-725
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Warner Lambert Participants:
Michael Barnett, D.D.S., Senior Director, Dental Affairs/Technology Development
Janet Firriolo, Ph.D., Senior Manager, Toxicology
Jane Zhang, Ph.D., Scientist, Oral Technology
Scott Harper, Ph.D., Director, Oral Technology Development
Lori Kumar, Ph.D., Director, Oral Care Research and Development
J. Tony McGuire, Senior Manager, Statistics and Data Management
Paul Okarma, Ph.D., Director, Regulatory Affairs
David Lore, Esq., Corporate Legal Affairs

Consultants:
Don Ridley, Cantox
Dominick Zero, D.D.S., Director, Oral Health Research Institute, Indiana University School of Dentistry

Meeting Objective: To discuss the proposed protocol dated November 17, 1999, regarding the use of a salivary fluoride level study to assess the efficacy of a Listerine/acidulated phosphate fluoride (APF) mouth rinse.

80N-0042

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BACKGROUND

Based on their wish to market an oral rinse product with both anticaries and antigingivitis, antiplaque claims and the Dental Plaque Subcommittee's (the Subcommittee) general recommendation that such a product would be a rational combination, the Warner-Lambert Company (W-L) requested a meeting to discuss the regulatory process to market such a combination product. At that meeting, held October 8, 1999, the dosing discrepancy between the anticaries final monograph and the Subcommittee's recommended monograph for antigingivitis, antiplaque products was discussed. W-L proposed to amend the anticaries monograph to allow for an alternate dosing regimen for fluoride rinses that would be consistent with the current labeled dosing for their Listerine product.

At the initial meeting, the W-L was advised to submit a citizen petition including data demonstrating the availability of fluoride in the proposed formulation and the effectiveness of the alternate fluoride dosing regimen. Further, W-L was invited to submit a protocol to establish efficacy of the proposed product/dosing regimen for Agency review.

W-L submitted a protocol for review on November 17, 1999. In this protocol, the efficacy of the proposed product/dosing regimen would be established using a surrogate endpoint of residual salivary fluoride levels was being proposed.

MEETING MINUTES

Following introductions, and a brief presentation by Paul Okarma, feedback was provided as follows:

1. A salivary fluoride level study causes concern, as it establishes a surrogate for caries testing. This is not a precedent the Agency is comfortable with. The change in the fluoride concentration of the proposed product and the proposed dosing regimen are both changes that are likely to affect efficacy. W-L would need to provide information to support the changes. Preliminary uptake studies, and surrogate endpoints may be supportive, but would not be conclusive. Historically, a full anticaries study would be required.

> *W-L response:* The surrogate test was suggested as a bioequivalence-type test to establish the availability to the active ingredient.

2. The monograph provides for a dosing regimen for fluoride rinses of 10 mL rinse for 60 seconds. The proposed dosing of 20 mL rinse for 30 seconds may be effective, but W-L needs to establish that this dosing regimen is bioequivalent. If, however, the 20mL concentration does not saturate better than the 10 mL concentration, the new dosing regimen would simply be decreasing the rinse time.

3. It is not clear whether the salivary flouride concentration has been validated as an acceptable study endpoint. If it is being used as a surrogate for efficacy, W-L will need to validate its ability

to discriminate. What is the advantage of this test over the intra-oral appliance test that W-L considered using.

> *W-L's response:* Literature and study models point to a relationship between salivary fluoride concentration and anticaries effect. This is an association, however, not a linear, cause/effect relationship. The salivary concentration test also takes into account the residual fluoride effect after the 30 second rinse.

4. Listerine has an excellent safety profile, but W-L will need to show that the adition of fluoride to the formulation doesn't change the safety.

ACTION ITEMS:

1. W-L will respond to the Agency's feedback, recognizing that the salivary concentration test may not be acceptable. Part of response will be submission of an alternative intra-oral appliance protocol.

2. Protocol will require a negative control and a reference product. Should also have a rinsing arm to the study.

Minutes Preparer: _____
Kerry Rothschild, Esq.
Project Manager

Meeting Chairperson: _____
Robert Sherman, IDS

cc: Docket Number 80N-0042
HFD-560/Office files
HFD-560/Ganley/Katz/Lumpkins/Neuner/Sherman/Mason/Rothschild
HFD-540/Kelsey/Hyman
HFD-725/Linst/Lee
Warner Lambert Company

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: APR 20 2000

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 80N-0042

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☐ This material should be cross-referenced to Comment No. _____

Charles J. Ganley, M.D.

Attachment